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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,672	10/17/2005	Yoshiki Kawabe	KAWABE1	1850

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EXAMINER	
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ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,672	KAWABE ET AL.	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7,10,16 and 21-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 7, 10, 16, 21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/30/2008 has been entered.

Status of the claims

2. Claims 15 and 17-20 were cancelled in the amendment of 10/30/2008; claims 1, 4, 7, 10, 16, 21 and 22 were amended and claims 23-25 are new. Claims 1, 4, 7, 10, 16, 21-25 are pending and currently under examination.

Claim Objections

3. Claims 16 and 25 are objected to because of the following informalities: In claim 16, line 4, the word "as" is duplicative. In claim 25, line 1, "The method o" should read "The method of". Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 4, 10, 16 and 21-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, in the independent claims 1, 4, 21 and 22, it is unclear how the administration of G-CSF to a diabetic patient for regeneration of the β cells **in** the islets of Langerhans are differentiating the bone marrow cells into β cells. Also, in claim 4 the preamble does not agree with the end of the claim. Therefore, the metes and bounds of the claim could not be determined. Claims 23-24 are rejected as dependent claims.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: treating of the collected stem cells with specific factors that enable them to differentiate into pancreatic β cells. "Differentiating" (as recited in the claim) does not represent a method step *per se* since a person of ordinary skill in the art would not know what exactly is encompassed by the word. Correspondingly, the metes and bounds of the claim could not be determined.

In claims 16 and 22, it is unclear how a disease can be treated by preventing it. Therefore, the metes and bounds of the claim could not be determined.

With respect to claim 25, the claim is indefinite for failing to indicate what particular cells are prevented from disruption.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 4, 21, 23 and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating for a method of treating diabetes comprising mobilization of bone marrow cells upon G-CSF treatment, treating the collected stem cells with various factors (growth factors, cytokines or interleukins) in order to differentiate them into β cells and then administering them to patients to repopulate the islets of Langerhans, does not reasonably provide enablement for regenerating the pancreatic β cells by *in vivo* administration of G-CSF and *in vivo* differentiation of the mobilized bone marrow cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a method for treating diabetes consisting of administering G-CSF in a composition to a diabetic patient for regenerating pancreatic β cells, wherein the G-CSF differentiates antilogous bone marrow cells into β cells. The composition may contain additional diabetes treating drugs.

The art is aware of treating diabetes with bone marrow mobilized by G-CSF treatment followed by the differentiation of bone marrow derived cells into pancreatic islet cells and administration of cells back to the patient where the cells are repopulating the islets of Langerhans (Hussain M -U.S Pub No. 20040136969). Yamaoka et al. (Biochem. Biophys. Res. Commun. 296, 1039-1043, 2002), in a review of the state of the art, teach that the techniques of β cells regeneration therapy can be classified as:

(1) *in vitro* regeneration therapy (where embryonic stem cells from another sources than the patient are differentiated *in vitro*),

(2) ex vivo regeneration therapy (where the cells used for regeneration are patients own cells which are collected, differentiated *in vitro* and then readministered to the patient), or

(3) *in vivo* regeneration therapy (p. 1041, right col. to p.1043, right col.)

With regard to the *in vivo* regeneration therapy, the reference teaches that the proliferation of β cells is stimulated by various secreted proteins, including insulin-like growth factors (IGFs)-I and II, PDGF, Growth hormone Prolactin. Other factors known to control the differentiation of the β cells are: TGFβ, TGFα, EGF, HGF, NGF, IGFs, VEGF, INGAP, Reg, TNFα, IL-6, INFγ, PTHrP and GLP-1 (Paris et al., Experim. Diab. Res. 5, 111-121, 2004- p.113, right col. first full paragraph). Thus, there is no mention

that G-CSF would be a viable treatment for the *in vivo* regeneration or producing of pancreatic islet β cells from bone marrow derived cells. The specification does not provide any guidance as to how the differentiation step can be performed *in vivo* by administration of G-CSF to a patient nor any working example is provided. In order to demonstrate the feasibility of the method *in vivo*, a skilled artisan would have to perform a considerable amount of experimentation.

Due to the large quantity of experimentation necessary to test the method claimed *in vivo*; the lack of direction/guidance presented in the specification regarding the performance of the method claimed *in vivo*; the absence of working examples directed to same; the state of the prior art which establishes the unpredictability of the method when performed with other factors than the ones known in the art, undue experimentation would be required of the skilled artisan to use the claimed invention in its full scope.

8. Claims 7, 16, 22 and 25 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of type II diabetes, does not reasonably provide enablement for prevention or treatment of type I diabetes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The claims are drawn to a method for preventing β cell disruption in pancreatic islets of Langerhans by administration of G-CSF to diabetic patients or to a

method of treatment of diabetes by inhibiting β cell disruption due to administration of G-CSF in a composition which may or may not comprise other drugs for treating diabetes.

While the art is aware of preventing of β cell disruption in pancreatic islets of Langerhans in diabetic patients (Bernard-Kargar et al., Diabetes, 50 (suppl. 1) S30-S35, 2001; Krakowski et al., J. Pathol. 16, 103-112, 2002). The art is silent for using the method for type I diabetes. This is because in the case of Type I diabetes the β cell are destroyed and there are no β cells present after diagnosis whose disruption needs to be prevented. Therefore the method as claimed, when interpreted as being directed towards Type I diabetic patients, is highly unpredictable and the preponderance of evidence indicate that the chances of its success are almost inexistent. The specification does not offer any guidance towards the use of the method foe Type I diabetes. There is no working example directed to this type of diabetes. It is therefore concluded that the amount of experimentation needed to establish this method is extremely high, given the extremely narrow chances of success.

Due to the large quantity of experimentation necessary to test the method claimed for the Type I diabetes patients; the lack of direction/guidance presented in the specification regarding the performance of the method claimed for these patients; the absence of working examples directed to same; the state of the prior art which establishes the unpredictability of the method when performed for type I diabetes, undue experimentation would be required of the skilled artisan to use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1, 4, 10, 16 and 23-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Hussain M (U.S Pub No. 20040136969, with an effective filling date of 10/02/2002).

Hussain teaches a subpopulation of bone marrow cells which are capable of differentiating into insulin-producing pancreatic islet cells and to a method for treating a diabetic condition by administering adult bone marrow derived stem cells which can differentiate and then function as pancreatic islet cells ([0003]). Also taught is a method for stimulating the mobilization of cells from bone marrow and the differentiation of bone marrow derived cells into pancreatic islet cells, by treating such bone marrow-derived cells with an effective stimulating amount of granulocyte colony stimulating factor (G-CSF) and/or granulocyte-macrophage colony stimulating factor (GM-CSF) .The method may be performed in conjunction with a method for treating a diabetic condition in a mammal, by administering a therapeutically effective amount of autologous bone marrow or an effective subpopulation thereof in combination with purified recombinant G-CSF or GM-CSF in an amount effective to stimulate the mobilization and

differentiation of some of the bone marrow cells into pancreatic islet cells ([0012]). The cells used in the method are adult bone marrow cells that have pluripotent differentiation capacity. Such cells, when transplanted, have the potential to restore function of certain endocrine cells to a patient who has lost such production due to disease such as diabetes mellitus. Thus bone marrow derived cells populate pancreatic islets of Langerhans. When purified from islets, said cells express insulin, the glucose transporter 2(GLUT2), and transcription factors typically found in pancreatic beta cells ([0022]). The teachings of Hussain established that bone marrow harbors cells that can differentiate into functionally competent pancreatic endocrine beta cells and thus represent a source for cell-based treatment for diabetes mellitus ([0023] and claims 14-17). The performing of the method for treating and/or preventing a diabetic condition in a mammal in need thereof by administering to the mammal a therapeutically effective amount of autologous or non-autologous bone marrow or an effective subpopulation thereof, wherein the autologous or non-autologous bone marrow, or effective subpopulation thereof, is administered with purified recombinant G-CSF and/or GM-CSF in an amount effective to stimulate the mobilization and differentiation of some of the bone marrow cells into pancreatic islet cells ([0024]) would necessarily prevent the beta –cell disruption by the inherent properties of the G-CSF administered. Therefore, the teachings of Hussain anticipate the claims 1, 4, 10, 16 and 23-24 of the instant Application.

On page 6-10 of the Remarks filed with the request for continued examination, Applicant argues that the claims should not be rejected over the Hussain reference for the following reasons:

a) "The present invention is based on the discovery by the present applicants/inventors that when granulocyte colony- stimulating factor (G-CSF) is administered as a drug or agent for the treatment of diabetes, stem cells in autologous bone marrow increase in number, and are recruited and differentiated into β-cells in pancreatic Langerhans' islets. In addition, according to the present invention, it is unnecessary to administer bone marrow cells which are collected ex vivo." (p.6)

b) "Hussain does not at all describe the actual use of G-CSF. Therefore, Hussain does not even inherently or implicitly disclose the characteristic property of G-CSF according to the present invention. Hussain does not provide a disclosure which would enable one skilled in the art to reach applicants' claimed subject matter. "The method of Hussain requires administering bone marrow derived stem cells as an indispensable limitation. Therefore, the invention and disclosure of Hussain is quite different from the present invention in such indispensable feature." (p.8)

c) "the present invention is characterized in that (1) there is no need to collect stem cells after administration of a drug, and (2) to administer the collected stem cells to a diseased part, and also in that stem cells can be recruited by only the administration of G-CSF... which the invention of Hussain does." (p.9)

d) "Hussain does not at all teach or suggest that G-CSF has the advantage of increasing the number of stem cells." (p.10)

The arguments were carefully considered but not found persuasive because of the following reasons:

a*) The statement is factually incorrect since in the Application it is stated:

"[0042] The present invention further relates to a method for producing pancreatic Langerhans β cells, which is characterized by collecting stem cells after administering a stem cell-recruiting factor or factors, and then differentiating the collected stem cells into pancreatic Langerhans β cells.

[0043] Stem cells may be collected in a known manner, for example, by isolating mononuclear cells from the peripheral blood or by sorting blood having a stem cell marker such as CD34, c-kit or CD133 to give a stem cell fraction.

[0044]. The stem cells thus collected may be differentiated into pancreatic Langerhans β cells in any manner, for example, by culturing the stem cells in the presence of a differentiation-inducing factor for pancreatic Langerhans β cells, by treating the stem cells with a differentiation-inducing factor for pancreatic Langerhans β cells, or by growing the stem cells using cell fusion techniques.

[0045] The differentiation factor for pancreatic Langerhans β cells used in the present invention is not limited in any way as long as it allows differentiation of stem cells into pancreatic Langerhans β cells. Specific examples of such a factor include bFGF, Reg gene, TGF, IGF1, activin A, NGF, VEGF and interferons. "

b*) Hussain teaches the use of G-CSF as presented above ([003], [0012] and [0024] of the Hussain reference. Also, the collection of stem cells is detailed in the Application as presented immediately above.

c*) See point a* above.

d*) this limitation is not present in any claim. However, if it were, it would be noted that it was well known in the art at the time the invention was made that G-CSF increases the number of stem cells from bone marrow was a known fact in the art as evidenced by Takano et al. (Current Pharmaceutical Design, 2003, 9, 1121-1127-cited in the previous Office action).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. Claims 7 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krakowski et al. (J. Pathol. 16, 103-112, 2002- cited in the previous action) in view of Hussain M (U.S Pub No. 20040136969, with an effective filling date of 10/02/2002).

The claims are drawn to a method for preventing β - cell disruption in pancreatic Langerhans' islets, by administering G-CSF to a diabetic patient in need in an amount sufficient to provide the prevention.

Krakowski et al. teach a method of treatment of low-dose streptozocin induced diabetes by GM-CSF. Transgenic mice expressing GM-CSF in the pancreatic islets were protected from developing streptozocin induced diabetes and from cell disruption (Discussion section). The method is similar to the only working example in mice, provided in the Specification of the Application and with the exception of the fact that Applicant used G-CSF instead of GM-CSF, the results are the same.

The teachings of Hussain are presented supra. The fact that Hussain et al. contemplates the use of G-CSF interchangeably with GM-CSF provides evidence of the similar effects of the two colony stimulating factors.

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to have used G-CSF in the method of Krakowski et al. with a reasonable expectation of success because Hussain used the two colony stimulating factors interchangeably in a related method. A person of ordinary skill in the art is always motivated to pursue the known options within her or his technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense, as eloquently expressed in the Supreme Court decision in KSR International Co. v. Teleflex Inc., 550 US, 82 USPQ2d 1385 (2007).

15. Claims 1, 4, 7, 16 and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lukic et al. (Develop. Immunol., 6, 119-128, 1998- cited in the previous action) in view of Dalhoff et al. (J. Inf. Disease., 178, 891-895, 1998- cited in the previous action) and in further view of Maedler et al. (J. Clinical Investigation, 10, 851-860, 2002).

The claims are drawn to a method for treating diabetes or to regenerate β- cells or to prevent β- cells disruption, which essentially consists of the steps of administering G-CSF to a diabetic patient in need thereof in an amount sufficient to regenerate or promote regeneration of pancreatic Langerhans' islets of said patient wherein the G-CSF differentiates the bone marrow cells into β- cells.

Lukic et al. teach that the macrophages infiltrate the pancreatic islets in multiple low-dose streptozocin induced diabetes (the method is similar to the only working example in mice, provided in the Specification of the Application) (p. 120, left col. first

full paragraph). Also taught is the fact that IL-1 has toxic and destructive effects against β-cells (p.122, right col. last paragraph) The authors teach that treatment with IL-1 inhibitors (such as IL-1 receptor antagonist - IL-1 Ra) suppress development of diabetes (table II; p. 126, concluding comments). Lukic et al. does not teach the use of G-CSF for treatment of diabetes or protecting β-cells.

Maedler et al. teach that *in vitro* exposure of islets from nondiabetic organ donors to high glucose levels resulted in increased production and release of IL-1β and impaired β cell function. The IL-1 receptor antagonist (IL-Ra) protected cultured human islets from these deleterious effects. β cells themselves were identified as the islet cellular source of glucose-induced IL-1β. *In vivo*, IL-1β–producing β cells were observed in pancreatic sections of type2 diabetic patients but not in non diabetic control subjects. (abstract; p. 857, left col. second paragraph; and Figure 6). As such, IL-1 is identified not only in experimental induced diabetes model (Streptozocin induced) but also in diabetic patients. Also, IL-Ra is recognized as protector of β cells.

Dalhoff et al. teach that levels of the IL-1Ra are increased after administration of G-CSF to human patients (abstract).

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to have used G-CSF to increase the IL-1Ra levels to protect the β cells so as to treat their disruption/destruction and thus treat diabetes. The motivation to do so is implicitly present in the Maedler et al. since they show the benefic effects of IL-1Ra. The effect of using the G-CSF for differentiating the bone marrow cells into β-

cells is inherent to the use of G-CSF in the method, irrespective if it is an intended use or not since the properties of G-CSF are inherent to its structure.

On page 14 of the Remarks Applicant argues that the rejection over the Lukic et al. and Dalhoff et al. could not have made the invention obvious unless the Examiner used hindsight to combine them. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

16. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lu et al. (U.S. Pat. No. 6,610,535- cited in the previous action) in view of Forbes et al. (WO 02/50263, 06/27/2002- cited in the previous action).

The claims are drawn to a method for producing pancreatic Langerhans β-cells, which comprises the steps of: (a) collecting stem cells after administering G-CSF to a diabetic patient in need thereof; and (b) differentiating the collected stem cells into pancreatic Langerhans β-cells.

Lu et al. teach that Insulin-dependent diabetes mellitus (IDDM) is a good example of a disease that could be cured or ameliorated through the use of stem cells. They teach methods for the isolation and propagation of stem cells from virtually any tissue type. Such stem cells can then be used, for example, for direct transplantation or to produce differentiated cells *in vitro* for transplantation of pancreatic and hepatic stem cells that may serve as a source for many other, more differentiated cell types such as pancreatic beta cells (col. 2, line 67 to col.3 line 13). Lu et al. are silent about collecting stem cells from patients pretreated with G-CSF.

Forbes teaches a method of collecting stem cell after administering a composition called mobilizing composition comprising G-CSF (p. 5 lines 7-11). The stem cells are further used in a patient in need of tissue repair as in the case of diabetes mellitus (p. 19, lines 9-17).

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to have used the method of obtaining pancreatic beta cells as taught by Lu et al. after collecting the cells as taught by Forbes, to obtain the stem cells needed to be differentiated in Langerhans beta cells with a reasonable expectation of success because both methods have been successfully tested. The motivation to do so would have come from the suggestion of Forbes et al. which showed the benefits of autologous stem cell therapy.

17. Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lukic et al. (Develop. Immunol., 6, 119-128, 1998- cited in the previous action) in

view of Dalhoff et al. (J. Inf. Disease., 178, 891-895, 1998- cited in the previous action), Maedler et al. (J. Clinical Investigation, 10, 851-860, 2002) and Bonhomme et al. (U.S. Pat. No. 6,303,146- cited in the previous action).

The claims are drawn to a method for treating diabetes, which comprises the steps of: (a) administering G-CSF as active ingredient to a diabetic patient and (b) administering to the patient a diabetic drug selected from the group consisting of sulphonylurea drugs, biguanide drugs and thiazolysine derivative drugs, wherein the G-CSF differentiates the bone marrow cells into β- cells.

The teachings of Lukic et al., Dalhoff et al. and Maedler et al. (J. Clinical Investigation, 10, 851-860, 2002) were presented supra, together with the inherency rationale for G-CSF with respect to bone marrow cells. The references do not address the combination of the teachings with the administration of sulphonylurea drugs, biguanide drugs and thiazolysine derivative drugs.

Bonhomme et al. teach that oral antidiabetic drugs such as sulphonylureas and biguanidines are established forms of treatment for diabetes either alone or in combination (col. 1, lines 23-32).

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to combine the teachings of Lukic et al., Dalhoff et al. and Maedler et al. with the method of Bonhomme et al. to treat diabetes with a reasonable expectation of success because the methods were established in the art and it is obvious to combine two modalities of treatment with an expectation of a result at least as good as either modality alone. A person of ordinary skill in the art is always

motivated to pursue the known options within her or his technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Conclusion

18. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-18:00 M-Th and 8:30-18:00 alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/
Primary Examiner, Art Unit 1647